PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RG/G-33660A/BCK	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/001894	International filing date *(day/month/year)* 23.02.2005	Priority date *(day/month/year)* 24.02.2004

International Patent Classification (IPC) or national classification and IPC
INV. A61K31/43 A61K9/16 A61K47/26 A61K31/00

Applicant
SANDOZ AG

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.10.2005	16.05.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/001894

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-35 received on 20.10.2005 with letter of 10.10.2005

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 30
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 34 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 34 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-29,31-35
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29,31-35
Industrial applicability (IA)	Yes:	Claims	1-29,31-33,35
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 34 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: EP-A-0 080 862 (BEECHAM GROUP PLC) 8 June 1983 (1983-06-08)
D2: WO 2004/047808 A (LEK PHARMACEUTICALS D.D; KERC, JANEZ; SALOBIR, MATEJA) 10 June 2004 (2004-06-10)
D3: WO 03/063820 A (SANDOZ GMBH; SCHWARZ, FRANZ, XAVER) 7 August 2003 (2003-08-07)
D4: WO 00/66169 A (SMITHKLINE BEECHAM CORPORATION; CONLEY, CREIGHTON, PIERCE; DAVIDSON, N) 9 November 2000 (2000-11-09)
D5: US-A-4 177 254 (COOK, BRIAN ET AL) 4 December 1979 (1979-12-04)

If not indicated otherwise, the relevant passages are those mentioned in the International search report.

Assuming a valid priority of the present application, the P-document D2 cited in the International search report is not dealt with during the PCT-procedure.

Applicants attention is drawn to the fact that it is unclear, how new claims 16 ("or in combination") or 27 can refer to new claim 14 ("free of any other pharmaceutically acceptable excipient"). Claim 26 seems to be redundant.

Art. 33(2) The present application meets the requirements of Article 33(2) PCT, because the subject-matter of **claims 1-29 and 31-35** appears to be new in the sense of Article 33(2) PCT.

The prior art does not disclose an extrusion process using water as solvent or a granulate comprising micronized amoxicillin and a sugar and being free of further excipients.

Art. 33(3) The subject-matter of **claims 1-29 and 31-35** is not considered to involve an inventive step in the sense of Article 33(3) PCT.

D1 discloses a process for preparing a water-dispersible granulate comprising amoxicillin trihydrate and sugar. The granules are made by extruding the sieved mixture with dichloromethane (or other solvents), from which the subject-matter of **claims 1-29 and 31-35** differs in that water is used as solvent.

The problem to be solved by the present invention may therefore be regarded as how to provide a water-dispersible granulate comprising amoxicillin trihydrate.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of the remaining **claims 1-29 and 31-35** the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem

which could not have been foreseen by the skilled person.
Being aware of the teaching of D1 the skilled person performed an arbitrary choice out of one list containing all solvents for extrusion to select.
Since there is no surprising effect resulting from that choice, the solution proposed in **claims 1-29 and 31-35** of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

The differences in particle size distribution shown in figures 1 and 2 of the present application are so small, that it remains unclear which technical effect might be due to said differences.

Art. 33(4) The subject-matter of **claims 1-29, 31-33 and 35** is considered to be industrially applicable in the sense of Art. 33(4) PCT.

For the assessment of the present **claim 34** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/EP2005/001894

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/047808	10.06.2004	25.11.2003	26.11.2002

Claims

1. A process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising micronized amoxicillin trihydrate and a sugar, the process comprising the following steps:
   a. sieving the mixture of amoxicillin trihydrate and the sugar
   b. extruding said sieved mixture with water or aqueous solution of the sugar as granulation liquid to obtain a wet extruded mass
   c. screening the wet extruded mass through a sieve
   d. drying the sieved wet extruded mass
   e. dried and sieved extruded mass is homogenized to the granulate
   f. obtained granulate is dissolved in water to form smooth suspension immediately.

2. A process according to claim 1, wherein the sugar is selected from the group consisting of sucrose, lactose, sugar alcohols and maltodextrins alone or in combination.

3. A process according to claim 1, wherein the sugar is sucrose.

4. A process according to claim 2, wherein the sugar alcohol is manitol or sorbitol.

5. A process according to claim 1, wherein micronized amoxicillin trihydrate is present in from 1 to 80% by weight of the granulate.

6. A process according to claim 1, wherein micronized amoxicillin trihydrate is present in from 5 to 50% by weight of the granulate.

7. A process according to claim 1, wherein micronized amoxicillin trihydrate is present in from 10 to 30% by weight of the granulate.

8. A process according to claims 1 to 3, wherein sucrose is present in from 20 to 99% by weight of the granulate.

9. A process according to any one of claims 1 to 8, wherein the particle size of the granulate is in the range from 200 to 3000 µm.

10. A process according to claim 9, wherein the particle size of the granulate is in the range from 500 to 1500 µm.

11. A process according to any of claims 1 to 10, wherein no pharmaceutically acceptable excipient is added during the process.

12. A process as claimed in any of claims 1 to 10, wherein optionally pharmaceutically acceptabe excipient is added during the process.

13. A process for preparing free flowing granulate comprising micronized amoxicillin trihydrate and sugar for filling into glass bottles, unit dose sachets or into other suitable container, used for reconstitution into an aqueous suspension, which process comprises preparing granulates according to any one of the preceding claims.

14. A granulate comprising micronized amoxicillin trihydrate and a sugar, free of any other pharmaceutically acceptable excipient.

15. A granulate according to claim 14 for reconstitution into an aqueous suspension.

16. A granulate according to claims 14 to 15, wherein the sugar is selected from the group consisting of sucrose, lactose, sugar alcohols and maltodextrins alone or in combination.

17. A granulate according to claims 14 to 15, wherein the sugar is sucrose.

18. A granulate according to claims 14 to 16, wherein the sugar alcohol is manitol or sorbitol.

19. A granulate according to claims 14 to 18, wherein micronized amoxycillin trihydrate is present in from 1 to 80% by weight of the granulate.

20. A granulate according to claims 14 to 18, wherein micronized amoxicillin trihydrate is present in from 5 to 50% by weight of the granulate.

21. A granulate according to claims 14 to 18, wherein micronized amoxicillin trihydrate is present in from 10 to 30% by weight of the granulate.

22. A granulate according to claims 14 to 17, wherein sucrose is present in from 20 to 99% by weight of the granulate.

23. A granulate according to claims 14 to 17, wherein sucrose is present in from 70 to 90% by weight of the granulate.

24. A granulate according to any one of claims 14 to 23, wherein the particle size of a granulate is in the range of 200 to 3000 µm.

25. A granulate according to any one of claims 14 to 24, wherein the particle size of the granulate is in the range of 500 to 1500 µm.

26. A granulate according to claims 14 to 25, wherein the granulate contain no pharmaceutically acceptable excipient.

27. A granulate according to claims 14 to 25, wherein the granulate optionally contain pharmaceutically acceptable excipent.

28. A granulate according to claims 14 to 27, which is free flowing and which is provided in glass bottles, unit dose sachets or in other suitable container.

29. A granulate comprising micronized amoxicillin trihydrate and the sugar according to any one of claims 14 to 28, wherein the granulate is reconstituted with water into an aqueous suspension which can be swallowed by a patient.

30. cancel

31. A granulate according to claims 14 to 29, provided for pediatric use which is reconstituted with water into an aqueous suspension prior to use.

32. An aqeous suspension for oral administration to humans or animals comprising micronized amixicillin trihydrate and the sugar obtained after reconstitution of the granulate, prepared according to claims 1 to 13, with water into the aqueous solution.

33. A sachet product containing free flowing granulate according to claims 14 to 29, which comprises micronized amoxicillin trihydrate and the sugar in a suitable unit dose, for reconstitution with water into an aqueous suspension immediately prior to use.

34. A method of treatment of bacterial infections in humans or animals, which comprises the administration of the granulate comprising therapeutically effective amount of micronized amoxicillin trihydrate and the sugar.

35. The use of granulate comprising micronized amoxicillin trihydrate and the sugar according to claims 14 to 29 in the manufacture of a medicament for treating bacterial infections.